Treatment of Disorders of Sodium Balance in Chronic Kidney Disease

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Extracellular fluid volume expansion is nearly universal in patients with CKD. Such volume expansion has features similar to the syndrome of heart failure with preserved ejection fraction, which not only leads to symptoms but can also lead to further organ damage. Unique treatment challenges are present in this patient population, including low glomerular filtration, which limits sodium chloride filtration, intrinsic tubule predisposition to sodium chloride retention, and proteinuria. In addition, pharmacokinetic considerations alter the disposition of diuretics in patients with CKD and nephrotic syndrome. Maintaining extracellular fluid volume near to normal is often necessary for hypertension treatment in this population, but it may also help prevent progressive cardiovascular and kidney damage. Although powerful diuretics can often accomplish this goal, this often comes at a cost of competing adverse effects. An approach to reduce extracellular fluid volume while avoiding adverse effects, therefore, requires a nuanced yet aggressive therapeutic approach.

Key Words: Diuretics, Salt-sensitive hypertension, Nephrotic syndrome, Extracellular fluid volume expansion

INTRODUCTION

Disordered extracellular fluid (ECF) volume is nearly universal in CKD and typically presents with 1 of 3 common patterns. The most common includes mild ECF volume expansion, with salt-sensitive hypertension and left ventricular hypertrophy as predominant signs, but CKD can also present with more severe ECF volume expansion, typically together with the nephrotic syndrome. Less well recognized, at least today, is that CKD may also have components of a salt-wasting syndrome, sometimes severe enough to cause ECF volume contraction. The pathogenesis of these disorders will be reviewed, followed by a discussion of treatment.

Phenomenology of Salt Homeostasis in CKD

The rate at which kidneys excrete NaCl is related to the ECF volume and the blood pressure, which are therefore also related to each other. Although the nature of the relation between ECF volume and urinary NaCl excretion has been debated, Walser's summary of the literature suggested that human urinary NaCl excretion, at steady state, is normally a *linear function* of the ECF volume in excess of a critical value. The relation between NaCl excretion and ECF volume, therefore, describes a "kidney function curve" as shown in Figure 1A. The supporting human experiments were often conducted during several days to weeks, so that the tested persons were at steady state, with NaCl excretion equal to the NaCl intake (minus minor extrarenal losses). Recent work by Titze and colleagues has added nuance to these precepts, showing that sodium chloride excretion is more variable than previously appreciated, when measured on a daily basis,[1] and that there is more sodium storage outside ECF than previously understood.[2] Sodium storage in the skin associates with left ventricular hypertrophy in CKD.[3] Furthermore, in longer studies, it appears that some of the initial gains in ECF volume may dissipate over time.[4] Nevertheless, all agree that, in normal humans, "on a long-term basis, indeed what goes in also comes out,"[5] satisfying the law of mass balance. Furthermore, even in the studies by Rakova and colleagues, markers of ECF volume expansion remained suppressed when dietary salt intake is high,[4] suggesting that dietary NaCl loading does expand the ECF volume chronically; as noted subsequently, this relationship is exaggerated in CKD.

Guyton[6] demonstrated that renal salt excretion plays a central role in setting the mean arterial pressure. According to their analysis, which is related to, but distinct from Walser's, the relation between mean arterial pressure and urinary NaCl excretion at steady state is also nearly linear through a wide range of dietary salt intake; in fact, only very small changes in mean arterial pressure are required to produce substantial natriuresis (see Fig 1B). The relationship between mean arterial pressure and sodium excretion defines a different, but closely related, kidney function curve,[6] and the effect of arterial pressure on urinary NaCl excretion has been called the *pressure natriuresis*.

These models are essentially phenomenological and do not provide specific insight into physiological control mechanisms. Both models, however, have been corroborated by experimental data and accurately describe renal salt homeostasis under many conditions. They also have interesting implications for understanding renal salt retention and renal salt-wasting disorders. For example, the slope of the relation between ECF volume and renal salt excretion (the "time constant," Fig 1A) determines the speed with which an individual can adapt to a change in dietary intake. The slope appears to be reduced by aging and CKD (Fig 1A).[7] This means that it takes longer for the kidney to adapt to a change in dietary NaCl intake when

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kidney function is compromised or an individual is aged (see Fig 2). Thus, if dietary salt intake is reduced suddenly, ECF volume will decline more in older individuals and in individuals with CKD than in younger individuals with normal kidney function. Surprisingly, a reduced slope of the relation between ECF volume and dietary NaCl intake also predicts that the ECF volume will be increased when the dietary NaCl intake is normal or high in such patients.[8] This is the reason that individuals with CKD so often have ECF volume expansion and respond to dietary NaCl restriction with a marked decline in blood pressure. On the typical NaCl-rich "Western" diet, the kidneys' slow responses shift the kidney function curve downward and to the right (Fig 1B). If dietary salt intake is reduced suddenly, however, salt wasting may occur.

Another important implication of the relation between ECF volume (or mean arterial pressure) and renal salt excretion is that salt wasting may be present despite a preserved ability to reduce urinary salt excretion to negligible levels.[9] Clinical and experimental examples of salt-wasting disorders in which urinary NaCl excretion can be very low include the Mendelian disease, Gitelman syndrome, which is caused by loss of function of the thiazide-sensitive NaCl cotransporter. This observation indicates that the diagnosis of salt wasting relies on the ability to estimate the ECF volume precisely. Because such determinations are nearly always imprecise clinically, the diagnosis of subtle renal salt wasting may be difficult.

CLINICAL SUMMARY

- CKD is most commonly associated with expansion of the extracellular fluid volume, which typically contributes to hypertension.
- Loop diuretics are often required to reduce extracellular fluid volume and correct hypertension, but thiazide and thiazide-like diuretics may be more useful than previously appreciated.
- Nephrotic syndrome presents additional challenges to diuretic treatment, owing to the hypoalbuminemia and albuminuria.

Diuretics in CKD

Loop diuretics are typically drugs of first choice for treating ECF volume expansion in patients with CKD, as discussed subsequently. As shown in Figure 3, CKD alters the effectiveness of these diuretics in several ways. First, loop (and thiazide) diuretics are organic anions that reach their sites of action in the lumen of the thick ascending limb via secretion along the proximal tubules. The primary transport proteins involved, at the basolateral membrane, are organic anion transporters. Deletion of these proteins in mice produces diuretic resistance by inhibiting diuretic secretion into the tubule lumen.[10] These transport processes are relatively nonspecific, and a single transporter type can facilitate the movement of a variety of similarly charged molecules into the tubular lumen. Accordingly, any exogenous or endogenous substance that competes with a diuretic for one of these transport processes can potentially limit the efficient arrival of that diuretic to its site of action. Uremic anions are examples of endogenous substances that compete with loop and thiazide diuretics for tubular secretion, and the dose-response curve of these diuretics in CKD is shifted to the right (Effect A in Fig 3).[11] This means that higher doses are required to present the same diuretic concentration to its active site.

A second, perhaps more important, effect of CKD, however, is related to the loss of NaCl filtration. Although enhanced NaCl reabsorption by tubules is typically the primary cause of ECF volume expansion as glomerular filtration rate (GFR) declines, the amount of sodium chloride reabsorbed by each nephron must also decline, to maintain sodium chloride excretion equal to intake. This decline limits the effects of blocking sodium chloride reabsorption with diuretics. Viewed another way, the basal fractional sodium excretion increases as CKD progresses (Effect 2 in Fig 3A) to maintain sodium chloride balance. This means that, although the maximal *fractional* rates of NaCl excretion are

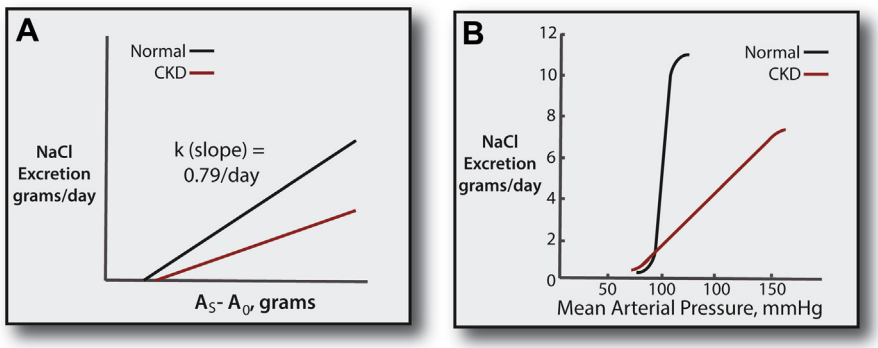

Figure 1. Kidney function curves in normal individuals and CKD. (A) Relationship between NaCl excretion and body sodium chloride content (A_S) greater than a basal value (A_0). This analysis is based on the study of Walser.[69] The slope of the normal relationship (k, which is a time constant) is taken from Walser's review of the literature. The slope appears to be reduced by CKD. (B) Classic kidney function curve as drawn by Guyton.[6] As argued by Guyton, CKD shifts the kidney function curve downward and to the right, describing the increased salt sensitivity in this population.